REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Claims 1-26, inclusive, have been cancelled without prejudice or disclaimer.

The new claims 27-51, inclusive, added by this amendment are fully supported in the specification as it was originally filed.

With respect to new claim 27, which corresponds to now cancelled claim 1, the polysaccharides have been limited to alginates and chitosans. In addition, the lack of any cross-linking in the complexes according to the invention (between the immunoglobulin and the polysaccharide and among the molecules of the polysaccharide) is now specifically recited to distinguish over the compositions of the prior art. The basis for the recitation in claim 27 of the lack of any cross-linking or reticulation, with respect to the claimed compositions, is to be found in experimental example n.2, at pages 12 and 13, as well as in the process for their preparation, found at page 11 of the specification, from which it is readily evident that no cross-linking or reticulating agent is added.

The present claim 28 corresponds to former claim 5.

In new claim 29, formerly claim 8, applicants inadvertently referred to "*a high degree of acetylation*". It has been corrected to now read "high degree of *deacetylation.*" The foregoing is supported at page 5, line 16 of the specification.

The composition claims formerly corresponding to claims 13-23 have been redrafted and are now numbered claims 34-42.

The composition underlying a therapeutic method (composition for use in the treatment of...) corresponding to former claims 24 and 25 have been reformulated appropriately in new claims 43-46. Former claim 25 has been also split according to the different kind of therapeutic methods. Support for the therapeutic methods is to be found at page 9, line 9 to page 10, line 20.

Claims 50 and 51 are new and depend on the compositions claim. They refer to the process for preparing complexes of polysaccharides and immunoglobulin. Support is to be found at page 11, lines 19-26.

With regard to item 4, the new set of claims now reads, "An isolated composition...". This serves to overcome the §101 rejection. Its withdrawal is respectfully solicited.

The new set of claims serve to overcome the §112, second paragraph, rejection.

With regard to item 6 of the Office Action, the trademark Protasan has been deleted from the claims.

With regard to item 7 of the Office Action, the terms "derivative or derivatives" in former claims 8-10 and 19 have been deleted. In former claim 22, now claim 38, the term "derived from *Corynebacterium*" has been replaced by "isolated from *Corynebacterium*".

With reference to item 8 of the Office Action, former claim 8, Applicants wish to point out that the definition of chitosan at a low or high degree of deacetylation is well-known to those skilled in the art since commercial chitosan is derived by deacetylation from chitin. The definition of chitosan with high or low degree of deacetylation refers therefore to a 100% degree of acetylation of chitin. Those skilled in the art are also aware of the definition of high and low molecular weight; high and low molecular weight

chitosan, obtained according to methods well known in the art, are for example defined in prior art documents, such as WO 98/30207, p. 6 of the specification and in the cited literature.

- **Claim rejection under 35 USC § 102**

Claims 1-7 and 10-13 stand rejected under §102(a) as anticipated by Gombotz et al. Claims 1-9 and 11-13 stand rejected under §102(b) as anticipated by Watts et al. Both rejections are respectfully traversed.

Neither of the references cited by the Examiner disclose the same two-component composition recited in claim 27, namely, (1) a polysaccharide selected from a chitosan or an alginate and 2) an immunoglobulin, wherein neither the polysaccharide molecules are cross-linked with each other or with the immunoglobulins.

In the new set of claims, Applicants in order to stress that the present composition does not involve any covalent bonding, have not included the term "***complex***" in claim 27.

By contrast, Gombotz specifically discloses **divalent ions cross-linked alginate complexes**. This is shown in Example 1 of the experimental section (col. 5, lines 17-18) describing the preparation of such complexes as involving the use of a **"cross linking divalent cation"**. At col. 5, table 1 the beads are defined as **"...alginate beads cross-linked with various divalent cation"**.

To improve the alginate beads and to further slow down the release of the active principle, Gombotz adds different polycations, such as poly-His, poly-Arg or poly-Lys, as shown at col. 6, table II. This embodiment is quite different from the Applicants' invention, because of the addition of a further component to the compositions.

Watts (WO98/30207) does not disclose compositions comprising only chitosan and the active principle, but instead a **three component mixture comprising chitosan, gelatin and the active principle.**

Therefore, the compositions according to claims 27-45 consisting of **polysaccharides and immunoglobulins, are distinguishable over and, therefore, not anticipated by either Gombotz et al. or Watts.**

It is respectfully submitted that the therapeutic methods and process for their preparation are also novel as depending directly or indirectly from independent claim 27 which is not anticipated. Withdrawal of the §102(a) and §102(b) rejections is solicited since a *prima facie* case of anticipation has not been established.

- **Claim rejection under 35 U.S.C. §103(a)**

Claims 1-26 stand rejected under §103(a) over Gombotz et al., and Watts et al., in view of Anderson et al., Griffith et al., Garner et al., and Costa et al. This rejection is respectfully traversed.

The prior art employed by the Examiner does not provide any suggestion for the preparation of compositions characterized by a polysaccharidic component which is neither cross-reticulated nor covalently bound to the immunoglobulin.

As discussed previously with respect to the §102 rejections, the addition of a third component, gelatin, as disclosed in Watts, serves to avoid the effect of chitosan cross-linking and results in microspheres which are similar to those obtained by reticulation. *"The effect is also similar to that obtained for partially aldehyde cross-linked chitosan microspheres,....* (Watts et al., p. 7, l. 23-25).

Therefore there is no suggestion in Watts to prepare compositions for mucosal transport by combining chitosan (as a polysaccharide) with the drug only, thus avoiding covalent links or cross-reticulation. The teaching is, in fact, rather the opposite, namely that the effect obtained by **chitosan cross-linking** is extremely *desirable* and that a similar effect is obtained **by the addition of gelatin**.

In Watts the composition may also comprise a suitable enteric coating material to prevent release until the formulation reaches the small intestine or the colon and to indicate that they are formulated in particular to achieve a "retarding effect" (for example see on p. 14, lines 6-8 and 10-30).

By contrast, in the present invention the polysaccharide forms a polymeric film which is resistant to enzymatic activity and which envelopes and protects the immunoglobulin from degradation, but the absence of cross-reticulation or of any covalent link, allows as a result thereof, to favor and enhance the absorption of the active principle in the composition through the mucosal membrane, as reported at p. 5, lines 18-31.

"Such polysaccharides or their derivatives are chosen among those which can form around the structure to be incorporated (in the specific case immunoglobulins) a polymeric "film" resistant to enzymatic activity and to chemico-physical variations in the digestive tract, and also enable the possibility to direct the incorporated substance towards mucosal cells, thus enhancing their absorption. .....A characteristic of the complexes according to the invention is that polysaccharides coat immunoglobulins without being linked to the latter by means of covalent bonds, but rather forming a sort of surface envelope i.e. in a gel form as in the case of alginic acid."

In summary, the polysaccharidic film according to the present invention, allows for the obtention of a composition ready for oral and transmucosal administration without

adding any cross-reticulating agents and with an optimal time of maximum release of from 3 to 6 hours, preferably 3 hrs (time of blood withdrawal, see p. 14, lines 23-24 and p. 15, line 12).

The lack of residues of any cross-reticulating agent as used in the prior art, represents a further advantage in the present invention, as stated in the specification, p. 5, l. 24-27: "*The absence of cross-linking between polysaccaride and Ig is a further advantage of the complexes according to the invention, since the method used for their preparation is easier and the final product does not contain any potentially toxic residue of the chemical cross-linking.*". This advantage can be easily extended to the lack of any cross-linking in the present compositions.

A further advantage is the ease of preparation of the claimed composition by the claimed process. The process simply involves mixing the particular polysaccharide (i.e. chitosan, modified chitosanes and alginate) with immunoglobulins, according to the process described at p. 11, l. 19-26 of the specification, and in new claim 52, as follows:

"*...the process for the preparation of the complexes of immunoglobulins and polysaccharides, in particular alginic acid, polymannuronic acid, methylglycolchitosane, chitosane with low molecular weight and high degree of deacetylation, comprising the mixing of a concentrated solution of immunoglobulins (5-50 mg/ml) in Na_2SO_4, brought to a temperature between 50 and 60°C with a solution containing the polysaccharides in a concentration between 0.1 and 10% by weight/volume and mixing by mechanical agitation at maximum speed*."

The teaching of Gombotz is directed to the use of **cross-reticulation by divalent cations.** In one embodiment, the retarded release effect obtained by **divalent cation reticulation is further increased** by adding a polycation to the compositions. The best

results are obtained with polyhistidine as shown in table II. In that instance, only 35% of the cumulative release of the active principle is achieved by simulating *in vitro* the acidic condition of the stomach in 0.1M HCl, 6 hour after administration.

Therefore, the Gombotz reference does not provide any suggestion or even a hint to avoid cross-reticulation in polysaccharidic compounds. On the contrary, cross-reticulation due to the further addition of polycations is further increased.

Also the disclosure of Watts in light of Gombotz, points to the importance of cross-linking in the polysaccharidic components of the compositions, and when this is not achieved, as disclosed in Watts, a further component (gelatin) is necessary to achieve properties similar to those obtained with reticulation.

To further sustain the proposition that different cross reticulated compositions provide different times of release, the Examiner is asked to note that the divalent cation cross-reticulated compositions disclosed in Gombotz, improved the polyhistidine release of the active principle only 35%, 6 hours after acidic treatment (see table II, line 29), while in the present invention the maximal effect (maximal average OD values in Tables 1-13) is measured 3-6 hours after *in vivo* administration (time of blood withdrawal, see p. 14, l. 23-24).

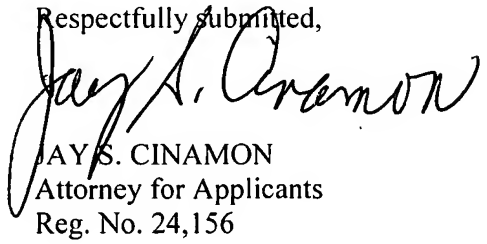
In no other reference cited by the Examiner can any suggestion be found referring to the possibility of preparing a polysaccharidic coating for an immunoglobulin while avoiding cross-reticulation.

Therefore new independent claim 27 and the claims dependent thereon distinguish over the combination of art cited by the Examiner. Accordingly, the §103(a) rejection has been overcome since a *prima facie* case of obviousness has not been established.

The issuance of a Notice of Allowance is respectfully solicited.

Please charge any fees which may be due to our Deposit Account No. 01-0035.

Respectfully submitted,



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